BEST AVAILABLE COPY

Nateglinide effectively controls prandial glycemia in subjects with impaired glucose tolerance

Christiane Guitard, Patrick Brunel, Monique Hoyer, Eckhard Pecher, James Agnew

Novartis Pharma AG Basel, Switzerland; Novartis Pharma, Australia

ABSTRACT

Background: Nateglinide (NAT) is an insulin secretion enhancer with a rapid onset and short duration of action. This 8-week randomized, double-blind study was carried out to evaluate the safety, tolerability and pharmacodynamic effects of NAT in subjects with impaired glucose tolerance (IGT).

Methods: Subjects with IGT (2-hour post-oral glucose tolerance test glucose ≥7.8 mmol/l and fasting plasma glucose [FPG] <7 mmol/l) were randomized into 4 groups: placebo (n=43), NAT 30 mg (n=83), 60 mg (n=76) and 120 mg (n=86), administered orally before meals (a.c.). Glucose and insulin plasma concentrations were measured at baseline (BL) and at 8 weeks following a standardized meal. Subjects experiencing symptoms of hypoglycemia during the study were to take a fingerstick blood glucose sample for confirmation.

Results: Compared to BL, all NAT doses enhanced early insulin secretion (at 30 minutes, the average insulin concentrations increased by 36–60% from BL), shifting the insulin concentration vs time curve to the left. At 120 and 180 minutes, insulin values were back to baseline levels. Statistically significant reductions (p≤0.0001) were seen with all three NAT dose groups compared to placebo in change from BL in the area-under-the-curve (AUC_{0-3}) for prandial glucose. The mean decrease from BL in 2-hour glucose values ranged between 0.77–1.29 mmol/l in the NAT groups. No marked effects on FPG were observed. Confirmed symptomatic hypoglycemia (blood glucose level ≤3.3 mmol/l) was seen in 1 (2.3%), 0, 5 (6.6%) and 21 (24.4%) subjects in the placebo and NAT 30, 60 and 120 mg groups, respectively. All symptoms were mild, did not require treatment or external help and only led to discontinuation in 3 NAT subjects (2.3%), 1 subject on 60 mg and 2 on 120 mg a.c.

Conclusions: NAT increases early insulin secretion and decreases peak glucose concentrations after a meal in IGT subjects. NAT was well tolerated in IGT subjects at doses of 30 and 60 mg a.c.

INTRODUCTION

The term impaired glucose tolerance (IGT) refers to a metabolic stage intermediate between normal glucose homeostasis and type 2 diabetes. Individuals with IGT are characterized by an elevated 2-hour glucose (7.8–11.1 mmol/l) following a 75 g oral glucose tolerance test (OGTT) and a fasting glucose value not meeting the diagnostic criteria for type 2 diabetes (fasting plasma glucose [FPG] <7.0 mmol/l). Many individuals with IGT are euglycemic in their daily lives and have normal or near normal glycated hemoglobin levels.[1] However, elevated 2-h OGTT is independently associated with all-cause mortality[2] and cardiovascular disease (CVD).[3] Although intensive lifestyle intervention (including diet and exercise) is effective in reducing progression to type 2 diabetes,[4] many subjects are unable to maintain lifestyle changes and would require pharmacologic intervention.

Nateglinide (Starlix®), a D-phenylalanine derivative, is a rapid-onset, short-duration insulin secretion enhancer. Taken just before a meal, nateglinide restores the physiologic insulin secretion pattern lost in IGT and type 2 diabetes, and prevents postprandial hyperglycemia with minimal risk of hypoglycemia.[6] Since impaired early-phase insulin release is a primary defect in type 2 diabetes and is associated with progression from IGT to diabetes,[9] an agent such as nateglinide that targets this defect may be effective in delaying or preventing development of type 2 diabetes.

The aim of this current study was to evaluate the safety, efficacy and tolerability of nateglinide in pre-diabetic subjects and to find a suitable dose for use in the large prospective study assessing the effect of nateglinide on progression to diabetes and prevention of cardiovascular morbidity and mortality (NAVIGATOR [Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research]). In the current study, the effects on insulin and glucose concentrations of three fixed doses of nateglinide (30, 60 and 120 mg) administered orally before meals (a.c.) were compared with placebo (a.c.) in individuals with IGT.

METHODS

Study design

- This was a multicenter, double-blind, randomized, parallel-group, dose-ranging study.
- Study subjects were randomized to one of four double-blind treatment groups in the ratio 2:2:2:1 for 8 weeks (Figure 1)
  - Nateglinide 30 mg a.c.
  - Nateglinide 60 mg a.c.
  - Nateglinide 120 mg a.c.
  - Placebo a.c.

Subjects

- Men or women with IGT. All subjects continued on their usual diet.
- Key inclusion criteria
  - Two 2-h OGTT ≥7.8 mmol/l (an amendment allowed the entry of subjects with 2-hr OGTT >11.1 mmol/l but only a small number of such cases were included in the study)
  - FPG <7 mmol/l.
- Key exclusion criterion
  - Subjects receiving prior or concomitant oral hypoglycemic therapy.

METHODS (cont'd)

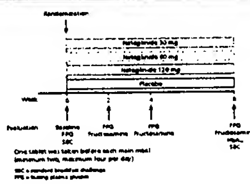

Randomization
Nateglinide 30 mg
Nateglinide 60 mg
Nateglinide 120 mg
Placebo
Week
0
2
4
8
Evaluation
Baseline
FPG
SBC
FPG
Fructosamine
FPG
Fructosamine
FPG
Fructosamine
HbA_{1c}
SBC
One tablet was taken before each main meal
(minimum two, maximum four per day)
SBC = standard breakfast challenge
FPG = fasting plasma glucose

Figure 1. Study design.

Safety endpoints

- Incidence of severe hypoglycemia (grade II symptoms, i.e, requiring external help).
- Number of discontinuations due to hypoglycemia
- Incidence of confirmed hypoglycemic events (blood glucose ≤3.3 mmol/l corresponding to plasma glucose of ≤3.7 mmol/l)
- Incidence of other adverse events (AEs)
- Laboratory evaluations.

Efficacy endpoints

- Efficacy variables
  - Change from baseline at Week 8 in plasma glucose levels determined over 3 hours following standard breakfast challenge (SBC).
  - Change from baseline at Week 8 in insulin levels determined over 3 hours following SBC.
  - Change from baseline at Week 8 in FPG, HbA_{1c} and fructosamine.

Standard breakfast challenge (SBC)

The 500 kcal breakfast meal was composed of orange juice (180 ml), toasted bread (60 g), jam or preserves (20 g), butter or margarine (10 g), and whole milk (120 ml) with coffee or tea (with non-nutritive sweetener) if desired.

Statistical analysis

- Binomial tests on the incidence of severe hypoglycemia and incidence of discontinuations for hypoglycemia
- Analysis of covariance of change from baseline at Week 8 on the intention-to-treat (ITT) population for postprandial glucose (PPG) (AUC_{0-3}), postprandial insulin, FPG, HbA_{1c} and fructosamine
  - General linear models used to evaluate efficacy variables for each active treatment arm vs placebo
  - Center and baseline were covariates.

RESULTS

Baseline demographics

Table 1. Baseline characteristics of randomized subjects

	Nateglinide 30 mg a.c.	Nateglinide 60 mg a.c.	Nateglinide 120 mg a.c.	Placebo a.c.
Number	83	76	86	43
Sex, n (%)				
Male	34 (41.0)	32 (42.1)	36 (41.9)	19 (44.2)
Female	49 (59.0)	44 (57.9)	50 (58.1)	24 (55.8)
Race, n (%)				
Caucasian	82 (98.8)	76 (100.0)	86 (100.0)	42 (97.7)
Asian/Oriental	1 (1.2)	0	0	1 (2.3)
Mean age, years (range)	56.4 (28–78)	57.6 (32–85)	57.2 (32–78)	58.4 (34–82)
Mean body mass index (BMI, kg/m²) (range)	30.2 (21–44)	30.4 (20–49)	30.0 (21–74)	30.2 (24–52)

RESULTS (cont'd)

Safety

Incidence of confirmed hypoglycemia

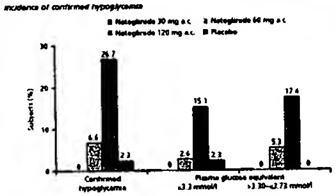


Figure 2. Percentage of subjects with confirmed hypoglycemia.

Incidence of other adverse events

Table 2. Number (%) of subjects with common (≥3% in any nateglinide group) AEs

Treatment (n)	Nateglinide 30 mg (n=83)	Nateglinide 60 mg (n=76)	Nateglinide 120 mg (n=86)	Placebo (n=43)
Total number (%) of subjects with at least one AE	31 (37.3)	25 (32.9)	44 (51.2)	13 (30.2)
Sweating increased, n (%)	4 (4.8)	1 (1.3)	14 (16.3)	1 (2.3)
Weakness, n (%)	3 (3.6)	5 (6.6)	11 (12.8)	2 (4.7)
Headache NOS, n (%)	3 (3.6)	8 (10.5)	6 (7.0)	3 (7.0)
Dizziness (excluding vertigo), n (%)	5 (6.0)	5 (6.6)	8 (9.3)	0
Tremor NEC, n (%)	2 (2.4)	2 (2.6)	7 (8.1)	1 (2.3)
Nasopharyngitis, n (%)	2 (2.4)	5 (6.6)	1 (1.2)	1 (2.3)
Influenza, n (%)	5 (6.0)	3 (3.9)	2 (2.3)	2 (4.7)
Fatigue, n (%)	1 (1.2)	1 (1.3)	5 (5.8)	0
Abdominal pain upper, n (%)	0	4 (5.3)	1 (1.2)	0
Nausea, n (%)	0	2 (2.6)	3 (3.5)	0
Vision blurred, n (%)	0	0	3 (3.5)	0
Hunger, n (%)	0	0	3 (3.5)	0

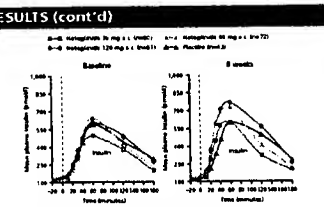
AE = adverse event, NOS = not otherwise specified, NEC = not elsewhere classified

Efficacy

Primary endpoints

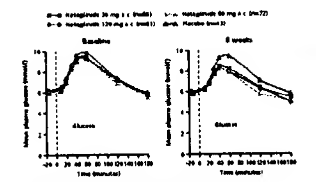
- Following SBC, all three doses of nateglinide enhanced early insulin secretion compared with baseline and placebo, shifting the insulin concentration vs time curve to the left (Figure 3).
- Insulin concentrations returned to baseline levels after 120–180 minutes.
- The nateglinide 60 and 120 mg a.c. doses showed similar efficacy and were more effective at stimulating early insulin release than the nateglinide 30 mg a.c. dose.
- Following SBC, all three doses of nateglinide decreased peak plasma glucose concentrations by ≥1 mmol/l, compared with baseline and placebo (Figure 4).
- The mean decreases from baseline in PPG concentration over 3 hours (AUC_{0-3}) are shown in Table 3.

RESULTS (cont'd)



p≤0.05 for nateglinide 120 mg only at 8 weeks compared with placebo

Figure 3. Postprandial insulin exposure following SBC in IGT subjects treated with nateglinide or placebo at baseline and Week 8.



p≤0.001 for all nateglinide doses at 8 weeks compared with placebo

Figure 4. Postprandial glucose exposure following SBC in IGT subjects treated with nateglinide or placebo at baseline and Week 8.

Table 3. Decrease from baseline in PPG concentrations AUC_{0-3} (h*mmol/l)

Treatment	Number†	LSM change from baseline (SE)	Difference from placebo
Nateglinide 30 mg a.c.	48	−1.62 (0.34)	−2.12*
Nateglinide 60 mg a.c.	66	−2.61 (0.34)	−3.11*
Nateglinide 120 mg a.c.	72	−2.62 (0.33)	−3.12*
Placebo	38	0.50 (0.44)	

*p<0.001,
†Number of subjects with observations at both baseline and endpoint
LSM = least squares mean
SE = standard error

Secondary endpoints

- Changes in FPG from baseline at Week 8 were not significantly different from placebo in any of the nateglinide groups (Table 4).
- Baseline HbA_{1c} in this population was in the normal range. Reductions in HbA_{1c} from baseline at week 8 were significant only in the nateglinide 120 mg group.
- Reductions in fructosamine from baseline at Week 8 were statistically significant for all three nateglinide groups, and were greatest in the nateglinide 60 mg group.

RESULTS (cont'd)

Table 4. Changes in FPG, HbA_{1c} and fructosamine levels from baseline at Week 8

Treatment	Number†	Baseline mean (SE)	LSM change from baseline (SE)	Difference from placebo
FPG (mmol/l)				
Nateglinide 30 mg a.c.	79	6.09 (0.08)	−0.06 (0.06)	−0.05
Nateglinide 60 mg a.c.	72	5.88 (0.08)	0.04 (0.07)	0.04
Nateglinide 120 mg a.c.	81	6.20 (0.08)	−0.03 (0.06)	−0.03
Placebo	43	6.20 (0.15)	−0.01 (0.09)	
HbA_{1c} (%)				
Nateglinide 30 mg a.c.	76	5.76 (0.06)	−0.15 (0.04)	−0.08
Nateglinide 60 mg a.c.	68	5.70 (0.06)	−0.12 (0.04)	−0.05
Nateglinide 120 mg a.c.	79	5.87 (0.07)	−0.19 (0.04)	−0.13*
Placebo	39	5.78 (0.10)	−0.06 (0.05)	
Fructosamine (µmol/l)				
Nateglinide 30 mg a.c.	79	248.8 (3.02)	−8.27 (2.02)	−6.83*
Nateglinide 60 mg a.c.	71	251.2 (3.69)	−8.62 (2.11)	−7.18*
Nateglinide 120 mg a.c.	81	258.4 (2.63)	−8.12 (2.04)	−6.67*
Placebo	43	254.2 (4.71)	−1.44 (2.65)	

*p<0.05
†Number of subjects with observations at both baseline and endpoint

SUMMARY

- Nateglinide 30 mg and 60 mg a.c. doses were associated with a low incidence of hypoglycemia and all events were mild.
- Apart from hypoglycemia and its symptoms the AE profile of nateglinide was similar to that of placebo
- All doses of nateglinide (30, 60 and 120 mg a.c.) showed increased early insulin secretion patterns compared with baseline and placebo. Insulin secretion was dose-dependent but of short duration. Insulin secretion did not exceed the meal period, with insulin values in the nateglinide groups similar to those in the placebo group 3 hours after SBC
- All doses of nateglinide decreased peak glucose concentrations by ≥1 mmol/l and showed reduced PPG concentrations (AUC_{0-3}) compared with baseline and placebo. The nateglinide 60 mg and 120 mg doses showed similar efficacy and had a greater effect than the 30 mg dose
- All doses of nateglinide produced statistically significant reductions in fructosamine at Week 8 compared with baseline.
- A significant reduction in HbA_{1c} was observed with nateglinide 120 mg despite baseline HbA_{1c} values in the normal range and the short duration of the study

DISCUSSION

- This study shows that a 60 mg a.c. dose of nateglinide is well tolerated, effective and has an excellent safety profile in IGT subjects.
- The results of this study indicate that nateglinide improves the insulin secretion profile in IGT subjects and reduces postprandial hyperglycemia
- The modest effect of nateglinide on HbA_{1c} and FPG is expected in this population, with baseline HbA_{1c} and FPG values, since nateglinide mainly affects postprandial glucose; characteristics are desirable and make nateglinide particularly suitable to treat subjec
- This study provides support for the use of nateglinide in the large study in IGT subjects: the effect of nateglinide and valsartan on progression to diabetes and prevention of cardiovascular morbidity and mortality (NAVIGATOR trial)

REFERENCES

1. ADA. Diabetes Care 2002;25:213–29
2. The DECODE study group. Lancet 1999;354:617–22
3. The DECODE study group. Arch Intern Med 2001;161:397–404
4. Saltau B, et al. Diabetes Care 1998;21(3):389–7
5. Diabetes Prevention Program Research Group. N Engl J Med 2002;346:393–403
6. Hanefeld M, et al. Diabetes Care 2000;23:202–7
7. Weller YH, et al. Eur J Clin Pharmacol 2000;56(2):129–33
8. Hollander PA, et al. Diabetes Care 2001;24(6):983–8
9. Weyer C, et al. J Clin Invest 1999;104:787–94